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PATENT SPECIFICATION

NO DRAWINGS

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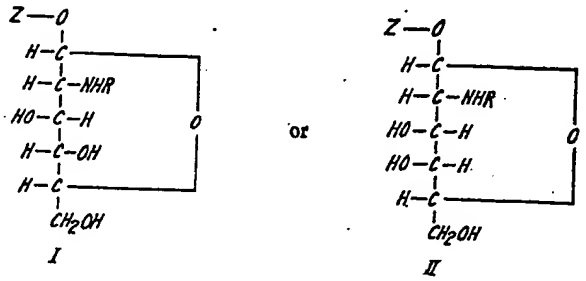
COMPLETE SPECIFICATION

Steroid 2'-Acylamino-2'-Deoxy-Glucosides and -Galactosides

We, MERCK & CO. INC., a corporation duly organized and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned generally with novel steroid 2' - acylamido - 2' - deoxy glucosides and their 4' - epimers, viz., 2' - acylamido - 2' - deoxy galactosides.

This invention provides novel compounds of formula



I or II

where R is a C_{1-3} alkanoyl radical and Z represents the residue of a 20 - keto - Δ^4 - (3 - keto or [3,2-c] - pyrazolo) - 11 - (keto, hydroxy or acyloxy) - 17α - (hydroxy or acyloxy) - 21 - hydroxy - steroid of the pregnane series from which the 21 - hydroxy group has been removed and in which any 16-hydroxy group is in free alcohol form or is formed, together with a 17α-hydroxy group, into a 16,17-acetomide, or the residue of a 20 - keto - Δ^4 - (3 - keto or [3,2-c] - pyrazolo) - 11 - (keto, hydroxy or acyloxy) - 17α - (hydroxy or acyloxy) - 16α,21 - dihydroxy steroid of the pregnane series from which the 16α-hydroxy group has been removed. Compounds represented by Formula I are glucoside derivatives and those represented by Formula II are galactoside derivatives. These novel steroid derivatives particularly 21-glucosides and 21-galactosides, possess the anti-inflammatory activity characteristic of cortisone but differ from cortisone, hydrocortisone, and their Δ^1 derivatives, prednisone and prednisolone, in being remarkably free from the ulcerogenic action, adrenal atrophy, thymus involution and body weight loss side-effects which have resulted from prolonged administration of the aforementioned anti-inflammatory steroids.

The invention also provides the tri-O-(C_{1-3} alkanoyl) derivatives of the novel 21-glucosides and their 4'-epimers.

In accordance with the present invention, the 2' - (C_{1-5} alkanoylamino) - 2' - deoxyglucoside of a 20 - keto - Δ^4 - (3 - keto or [3,2-c]pyrazolo) - 11 - (keto, hydroxy or acyloxy) - 17α - (hydroxy or acyloxy) - 21 - hydroxy - steroid of the pregnane series in which any 16 - hydroxy group is protected, e.g. by formation of a 16,17 - acetonide, or its 4' - epimer, is prepared by reacting the steroid with a 1 - halo - N - (C_{1-5} alkanoyl) - glucosamine tri(C_{1-6} alkanoate) or its 4'-epimer, thereby forming the tri-

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O - (C_{1-6} alkanoyl) - 2' - (C_{1-5} alkanoylamino) - 2' - deoxyglucoside of the 21-hydroxy steroid or its 4'-epimer, and reacting this tri - O - (C_{1-6} alkanoyl) compound with an alkaline hydrolysing agent.

Also in accordance with the present invention, the 2' - (C_{1-5} alkanoylamino) - 2' - deoxyglucoside of a 20 - keto - Δ^4 - (3 - keto or [3,2-c]pyrazolo) - 11 - (keto, hydroxy or acyloxy) - 17α - (hydroxy or acyloxy) - 16α,21 - dihydroxy steroid of the pregnane series, or its 4'-epimer, is prepared by reacting the steroid with an acylating agent to form the corresponding 16α - hydroxy - 21 - acyloxy compound, reacting the latter with a 1 - halo - N - (C_{1-6} alkanoyl) - glucosamine tri(C_{1-6} alkanoate) or its 4'-epimer, thereby forming the tri - O - (C_{1-6} alkanoyl) - 2' - (C_{1-5} alkanoylamino) - 2' - deoxyglucoside of the 16α-hydroxy steroid or its 4'-epimer, and reacting this tri - O - (C_{1-6} alkanoyl) compound with an alkaline hydrolysing agent.

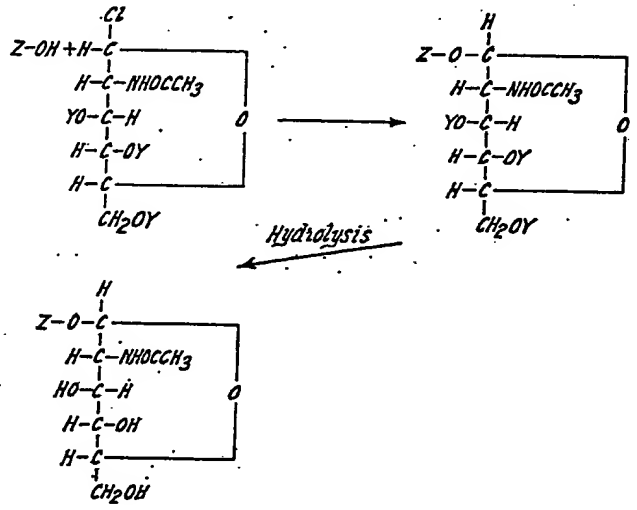
Another process in accordance with the present invention comprises reacting a 21 - [tri - O - (C_{1-6} alkanoyl) - 2' - (C_{1-5} alkanoylamino) - 2' - deoxyglucoside] of a 20 - keto - Δ^4 - (3 - keto or [3,2-c]pyrazolo) - 11 - (keto, hydroxy or acyloxy) - 17α - (hydroxy or acyloxy) - 21 - hydroxy - steroid of the pregnane series, or its 4' - epimer, with an alkoxide hydrolysing agent thereby forming the corresponding 21 - [2' - (C_{1-5} alkanoylamino) - 2' - deoxyglucoside] of the steroid.

Yet another process in accordance with the present invention comprises reacting a 16 - [tri - O - (C_{1-6} alkanoyl) - 2' - (C_{1-5} alkanoylamino) - 2' - deoxyglucoside] of a 20 - keto - Δ^4 - (3 - keto or [3,2-c]pyrazolo) - 11 - (keto, hydroxy or acyloxy) - 17α - (hydroxy or acyloxy) - 16α - hydroxy - 21 - acyloxy steroid of the pregnane series or its 4' - epimer with an alkoxide hydrolysing agent to form the corresponding 16 - [2' - (C_{1-5} alkanoylamino) - 2' - deoxyglucoside] of the corresponding 20 - keto - Δ^4 - (3 - keto or [3,2-c]pyrazolo) - 11 - (keto, hydroxy or acyloxy) - 17α - (hydroxy or acyloxy) - 16α,21-dihydroxy steroid.

The most convenient tri - O - (C_{1-6} alkanoyl) compounds are the O - tri - acetates and the reaction will be described using these compounds which will be referred to hereinafter as 1 - chloro - N - acetylglucosamine triacetate and 1 - chloro - N - acetylgalactosamine triacetate. The products formed by this reaction are 3',4',6'-triacetates, namely steroid - 21 - yl - tri - O - acetyl - β - D - 2 - acetamido - 2 - deoxy - glucosides and galactosides. The O - acetyl groups are then removed by hydrolysis.

As indicated above, the 16 - hydroxy derivatives are similarly prepared, the 21-hydroxy group being first protected by acylation. The hydrolysing step will remove the 21-acyl group as well as the O-acyl groups.

The reactions as applied to the preparation of glucosides may be represented as follows:



II

In the foregoing formulas Y stands for C_{1-6} alkanoyl and Z has the same meaning as above.

The O-triacetate derivatives are conveniently prepared by reacting the steroid substrate with 1-chloro-N-acetylglucosamine triacetate or 1-chloro-N-acetylgalactosamine triacetate in an inert organic solvent or solvent mixture in the presence of a dehydrohalogenation-promoting agent such as mercuric cyanide, mercuric iodide or silver carbonate and heating at an elevated temperature, preferably in an inert atmosphere. The product is separated from the reaction mixture and may be purified by chromatography on alumina.

The hydrolysis reaction, which is preferably carried out in an inert atmosphere is conveniently conducted by taking up the O-triacetate derivative in a lower alcohol such as methanol containing a metal alcoholate such as sodium methoxide and maintaining the mixture at room temperature for from ten minutes to an hour. The product is isolated by any convenient method. For example, the mixture can be adjusted to neutrality with a C_{1-6} alkanoic acid followed by the addition of water and cooling. The product which separates on cooling is usually crystalline and is recovered by filtration.

In accordance with those procedures, there are obtained N - acetamido - 2 - deoxy - glucosides and galactosides of, *inter alia*, the following steroids: cortisone, hydrocortisone, and the Δ^1-derivatives thereof, prednisone and prednisolone and their Δ^6 analogues; 16-hydroxy derivatives (including compounds in which the 16-hydroxy group is protected, e.g., by formation of a 16,17-acetonide) of any of the foregoing; and derivatives of any of these compounds having fluoro, chloro or bromo substituents attached to the 6,9,12 and/or 16-carbon atoms, and/or methyl substituents attached to the 2,6,12,15 and/or 16 carbon atoms. Of particular interest are the derivatives of 16-methyl cortisone and hydrocortisone especially the 6,16-dimethyl compounds and their Δ^6-derivatives and the [3,2-c]pyrazolo derivatives of such compounds.

The new compounds of this invention are stable and possess anti-inflammatory activity characteristic of cortisone but exhibit greatly reduced undesirable side effects. They are normally administered in a daily maintenance dosage range comparable with that of the parent steroid. For example, with the cortisone and hydrocortisone derivatives the daily dosage is about 25 to 75 mg., for prednisolone it is about 2.5 to 10 mg. and for dexamethasone 0.25 to 5 mg. Because of their selective anti-inflammatory action (substantially unaccompanied by undesired side effects) they may, in acute cases, be administered in substantially higher dosages without attendant risk of side effects; and, in milder conditions, may often be administered in substantially lower dosages in view of their pronounced anti-inflammatory action directly at the site of the inflammation.

The compounds of this invention may be administered alone or associated with a pharmaceutically acceptable carrier the choice of which will depend upon the chosen route of administration and standard pharmaceutical practice. For oral administration, the compounds may be administered in the form of tablets containing excipients such as starch or milk sugar. Aqueous solutions such as elixirs which may be sweetened by flavouring may also be employed. For parenteral use, isotonic mixtures in pyrogen-free water may be employed.

1 - Chloro - N - acetylglucosamine triacetate, which is used as a starting material in the preparation of the compounds of this invention in accordance with the process described above, is prepared by the following procdure.

A solution of 23 g. of clean sodium in 1000 ml. of methanol is used in 10 equal portions as described below; 21.5 g. of glucosamine hydrochloride and 100 ml. of the above solution are swirled in a 250 ml. Erlenmeyer flask for exactly 70 seconds. The sodium chloride which separates is removed by filtration under pressure through a sintered glass funnel with a 2 l. round bottom flask. This operation is repeated nine more times and the total filter cake washed with 100 ml. of methanol. The total filtrate in the flask is treated under nitrogen with 153 g. of acetic anhydride and warmed for a short time. The solution is then stirred for approximately fifteen hours during which time the N-acetylglucosamine precipitates in approximately 70% yield. It is recovered by filtration, washed extensively with methanol and dried to constant weight, m.p. 202—204°C.

This product is converted to the 1-chloro-O-triacetate derivative by the following procedure.

A suspension of 25 g. of N-acetylglucosamine and 70 ml. of acetyl chloride is stirred under nitrogen for ten minutes. At this point, 1 ml. of acetic acid saturated with HCl gas (as 0°) is added and after 15 minutes the mixture starts to reflux gently. At the end of two hours all of the material is in a yellow brown solution. The mixture is then stirred for approximately 15 hours, 500 ml. of chloroform is added, the mixture

poured into 1 kg. of ice and stirred for three minutes. (The balance of this procedure should be carried out as rapidly as possible to ensure maximum yields). The mixture is separated and the chloroform layer added rapidly to an ice cold saturated sodium bicarbonate solution with vigorous stirring. The slightly alkaline mixture is again separated and the chloroform layer washed once with water, dried over anhydrous sodium sulfate, filtered and the filtrate evaporated to dryness *in vacuo* at about 35°C. The residue is taken up in ethyl acetate at 55—60°C, filtered, seeded and the product allowed to crystallize overnight in the cold. The yield is 26.8 g. The product is protected from light and stored in a tightly stoppered container in the refrigerator.

1-Chloro-N-acetylgalactosamine triacetate is prepared as described hereinabove but starting with galactosamine hydrochloride instead of glucosamine hydrochloride.

The following examples illustrate this invention.

EXAMPLE I

11β,17α-Dihydroxy-3,20-Dione-1,4-pregnadiene-21-yl-β-D-2′-acetamido-2′-deoxy-glucopyranoside

A total of 4.5 g. of 11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione is taken up in 25 ml. of dry dimethylformamide containing 17.6 g. of mercuric cyanide and the mixture diluted with 25 ml. of dry xylene. A solution of 13.0 g. of 1 - chloro - N - acetylglucosamine triacetate in 100 ml. of 1:1 dimethylformamide-xylene is added dropwise over a period of three hours while stirring the mixture under nitrogen at an oil bath temperature of 130—135°C. The mixture turns quite dark during the addition. It is maintained at 130—135°C. for an additional one and three quarter hours, cooled, diluted with 500 ml. of chloroform and washed four times with 500 ml. portions of water. The aqueous layers are successively back-extracted with chloroform, the combined organic layers dried over anhydrous magnesium sulphate and filtered and the filtrate evaporated *in vacuo*. The residue is taken up in ethylene chloride and the solvent again removed *in vacuo*. The residue is then flushed twice with toluene and pumped (oil pump) at about 50°C for several hours and then at room temperature overnight. The residue is taken up chloroform and chromatographed on acid-washed alumina (only about 10.5 parts alumina/part of solution) keeping the height-to-diameter ratio of alumina in the column at about 8:1. The column is eluted with methanol-chloroform mixtures containing successively larger proportions of methanol up to 95:5. The product, 11β,17α - dihydroxy - 3,20 - dione - 1,4 - pregnadiene - 21 - yl - tri - O - acetyl - β - D - 2′ - acetamido - 2′ - deoxy - glucopyranoside is recovered from the middle fractions. Each fraction is taken to dryness. The first 2—3 fractions consist of a mobile oil. A small amount of methanol is added to subsequent fractions and those which crystallize on scratching are redissolved in chloroform, combined, filtered, taken to dryness and crystallized from ethanol.

A solution of 1.055 g. of the product thus prepared in 120 ml. of spectral grade methanol is treated with an equivalent quantity of freshly prepared sodium methoxide and kept at room temperature in a nitrogen atmosphere for ten minutes. The pH of the solution is adjusted to neutrality with acetic acid and the mixture filtered. About 6.5 ml. of water is added and the solution centrifuged. The desired product starts to precipitate in about ten minutes and the mixture is kept cold overnight. The desired product is recovered by filtration.

The procedure of the foregoing example is utilized to prepare 21 - yl - β - D - 2′ - acetamido - 2′ -deoxyglucopyranosides and galactopyranosides of the following compounds. In each instance the intermediate O-triacetate is prepared. The list is given to avoid unnecessary repetition of experimental details.

16α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione
16β-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione
9α-Fluoro-16α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione
9α-Fluoro-16β-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione
6α-Methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione
6α-Fluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione
6α,16α-Dimethyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione
6,16α-Dimethyl-11β,17α,21-trihydroxy-1,4,6-pregnatriene-3,20-dione
9α-Fluoro-11β,16α,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione
9α-Fluoro-6,16α-dimethyl-11β,17α,21-trihydroxy-1,4,6-pregnatriene-3,20-dione
17α,21-Dihydroxy-1-allopregnene-3,11,20-trione
9α-Fluoro-11β,17α,21-trihydroxy-1-pregnene-3,20-dione

11β,17α,21-Trihydroxy-[3,2-c]-pyrazolo-4-pregnen-20-one
11β,17α,21-Trihydroxy-2′-phenyl-[3,2-c]-pyrazole-4-pregnen-20-one
9α-Fluoro-11β,17α,21-trihydroxy-[3,2-c]-pyrazolo-4-pregnen-20-one
9α-Fluoro-16α-methyl-11β,17α,21-trihydroxy-[3,2-c]-pyrazolo-4-pregnen-20-one
16α-Methyl-11β,17α,21-trihydroxy-[3,2-c]-pyrazolo-4-pregnen-20-one
17α,21-Dihydroxy-1-allopregnene-3,11,20-trione
6,16α-Dimethyl-11β,17α,21-trihydroxy-[3,2-c]-pyrazolo-4,6-pregnadien-20-one
6,16α-Dimethyl-11β,17α,21-trihydroxy-2′-phenyl-[3,2-c]-pyrazolo-4,6-pregnadien-20-one
6,16α-Dimethyl-11β,17α,21-trihydroxy-4,6-pregnadiene-3,20-dione
6α-Fluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione
9α-Fluoro-6α,16α-dimethyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione

EXAMPLE II

9α-Fluoro-11β,17α,21-trihydroxy-3,20-dione-1,4-pregnadiene-16α-yl-β-D-2′-acetamido-2′-deoxy-glucoside

9 g. of 9α-fluoro-21-acetoxy-11β,16α,17α-trihydroxy-1,4-pregnadiene-3,20-dione is taken up in 50 ml. of dimethylformamide containing 36 g. of mercuric cyanide and the mixture diluted with 50 ml. of dry xylene. A solution of 1-chloro-N-acetylglucosamine triacetate in 200 ml. of 1:1 dimethylformamide-xylene is added dropwise over a period of three hours while stirring the mixture under nitrogen at an oil bath temperature of 130—135°C. The mixture turns dark during the addition. It is maintained at 130—135°C. for an additional two hours, cooled, diluted with one liter of chloroform and washed four times with 500 ml. portions of water. The aqueous layers are successively back-extracted with chloroform, the combined organic layers dried over anhydrous magnesium sulphate and filtered and the filtrate evaporated *in vacuo*. The residue is taken up in ethylene chloride and the solvent again removed *in vacuo*. The residue is twice flushed with toluene (oil pump) at about 50°C. for several hours and then at room temperature overnight. The product, 9α-fluoro-21-acetoxy-11β,17α-dihydroxy-3,20-dione-1,4-pregnadiene-16α-yl - tri-O-acetyl-β-D-2′-acetamido-2′-deoxy-glucoside is separated on acid-washed alumina using mixtures of chloroform and methanol.

This product is hydrolysed in accordance with the procedure of Example I to remove the three O-acetyl groups and the 21-acetyl group to obtain the desired product.

The procedure of the foregoing example is utilized to prepare 16α-yl-β-D-2-acetamido-2-deoxy-glucopyranosides and galactosides of the following compounds. In each instance the 21-hydroxy group of the steroid is first acylated and the intermediate O-triacetate of the glucosamine is prepared. The list is given to avoid unnecessary repetition of experimental details.

9α-Fluoro-11β,16α,17α,21-tetrahydroxy-4-pregnene-3,20-dione
9α-Fluoro-2-methyl-11β,16α,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione
6α,9α-Difluoro-2α-methyl-11β,16α,17α,21-tetrahydroxy-4-pregnene-3,20-dione
6α,9α-Difluoro-2-methyl-11β,16α,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione

The 16-mono-N-acetamido-2-deoxy-glucosides and galactosides of this invention are prepared from the corresponding 16-hydroxy-21-acylates such as the 21-acetate. The monoacetate is prepared as follows: a mixture of the 16,21-diacetate and the 21-monoacetate, prepared by treating the steroid substrate, for example 9α - fluoro - 11β,16α,17α,21 - tetrahydroxy - 1,4 - pregnadiene - 3,20 - dione, with 1.1 to 1.2 molar equivalents of acetic anhydride in pyridine, is extracted with an excess of 0.1M aqueous sodium tetraborate. The diacetate is insoluble. The 21-monoacetate dissolves in the alkaline solution and is precipitated on standing at room temperature after adjusting the pH to 1.2—2.0 with concentrated hydrochloric acid.

WHAT WE CLAIM IS:—

1. The process that comprises reacting a 20 - keto - Δ^4 - (3 - keto or [3,2-c] pyrazolo) - 11 - (keto, hydroxy or acyloxy) - 17α - (hydroxy or acyloxy) - 21 - hydroxy-steroid of the pregnane series in which any 16-hydroxy group is protected with a 1-halo - N - (C_{1-5} alkanoyl) - glucosamine tri (C_{1-6} alkanoate) or its 4′-epimer, thereby forming the tri - O - (C_{1-6} alkanoyl) - 2′ - (C_{1-5} alkanoylamino) - 2′ - deoxyglucoside of the 21-hydroxy steroid or its 4′-epimer, and reacting this tri-O-(C_{1-6} alkanoyl) compound with an alkaline hydrolysing agent to produce a 2′ - (C_{1-5} alkanoylamino) - 2′ - deoxyglucoside of the steroid or its 4′-epimer.

2. The process that comprises reacting a 20 - keto - Δ^4 - (3 - keto or [3,2-c] pyrazolo) - 11 - (keto, hydroxy or acyloxy) - 17α - (hydroxy or acyloxy) - 16α,21 - dihydroxy steroid of the pregnane series with an acylating agent to form the corresponding 16α - hydroxy - 21 - acyloxy compound, reacting the latter with a 1 - halo - N - (C_{1-6} alkanoyl) - glucosamine tri(C_{1-6} alkanoate) or its 4'-epimer, thereby forming the tri - O - (C_{1-6} alkanoyl) - 2' - (C_{1-6} alkanoylamino) - 2' - deoxyglucoside of the 16α-hydroxy steroid or its 4'-epimer, and reacting this tri - O - (C_{1-6} alkanoyl) compound with an alkaline hydrolysing agent to produce a 2' - (C_{1-6} alkanoylamino) - 2' - deoxyglucoside of the steroid or its 4'-epimer.

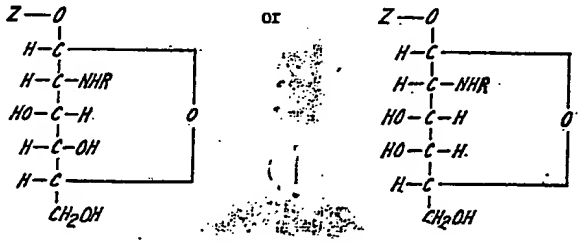
3. A process as claimed in claim 1, in which the glucosamine compound is a 1-chloro-N-(C_{1-6} alkanoyl)-glucosamine trialkanoate.

4. The process that comprises reacting a 21 - [tri - O - (C_{1-6} alkanoyl) - 2' - (C_{1-6} alkanoylamino) - 2' - deoxyglucoside] of a 20 - keto - Δ^4 - (3 - keto or [3,2-c] pyrazolo) - 11 - (keto, hydroxy or acyloxy) - 17α - (hydroxy or acyloxy) - 21 - hydroxy-steroid of the pregnane series, or its 4'-epimer, with an alkoxide hydrolysing agent thereby forming the corresponding 21 - [2' - (C_{1-6} alkanoylamino) - 2' - deoxyglucoside] of the steroid.

5. The process that comprises reacting a 16 - [tri - O - (C_{1-6} alkanoyl) - 2' - (C_{1-6} alkanoyl amino)-2'-deoxyglucoside] of a 20 - keto - Δ^4 - (3 - keto or [3,2-c]-pyrazolo) - 11 - (keto, hydroxy or acyloxy) - 17α - (hydroxy or acyloxy) - 16α - hydroxy - 21 - acyloxy steroid of the pregnane series or its 4'-epimer with an alkoxide hydrolysing agent to form the corresponding 16 - [2' - (C_{1-6} alkanoylamino) - 2' - deoxyglucoside] of the corresponding 20 - keto - Δ^4 - (3 - keto or [3,2-c]pyrazolo)-11-(keto, hydroxy or acyloxy) - 17α - (hydroxy or acyloxy) - 16α,21 - dihydroxy steroid.

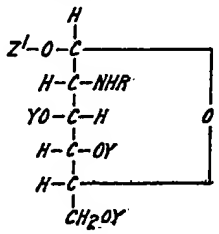
6. The process which comprises reacting 11β,17α,21 - trihydroxy - 1,4 - pregnadiene - 3,20 - dione with 1 - chloro - N - acetyl - glucosamine - triacetate thereby forming 11β,17α - dihydroxy - 1,4 - pregnadiene - 3,20 - dione - 21 - yl - tri - O - acetyl - β - D -2' - acetamido - 2' - deoxyglucoside, and reacting the latter compound with sodium methoxide thereby forming 11β,17α - dihydroxy - 1,4 - pregnadiene-3,20-dione - 21 - yl - β - D - 2' - acetamido - 2' - deoxyglucoside.

7. A compound having the general formula:



where R represents a C_{1-3} alkanoyl radical and Z represents the residue of a 20 - keto - Δ^4 - (3 - keto or [3,2-c]pyrazolo) - 11 - (keto, hydroxy or acyloxy) - 17α - (hydroxy or acyloxy) - 21 - hydroxy - steroid of the pregnane series from which the 21-hydroxy group has been removed and in which any 16-hydroxy group is in free alcohol form or is formed, together with a 17α-hydroxy group, into a 16,17-acetonide, or the residue of a 20 - keto - Δ^4 - (3 - keto or [3,2-c]pyrazolo) - 11 - (keto, hydroxy or acyloxy) - 17α - (hydroxy or acyloxy) - 16α,21 - dihydroxy steroid of the pregnane series from which the 16α-hydroxy group has been removed.

8. A compound having the formula:



or a 4'-epimer thereof, in which R is a C_{1-3} alkanoyl radical, Y is a C_{1-6} alkanoyl radical, and Z' is the residue of a 20 - keto - Δ^4 - (3 - keto or [3,2-c]pyrazolo) - 11 - (keto, hydroxy or acyloxy) - 17α - (hydroxy or acyloxy) - 21 - hydroxy - steroid of the pregnane series from which the 21-hydroxy group has been removed and in which any 16-hydroxy group is in free alcohol form or is formed, together with a 17α-hydroxy group, into a 16,17-acetonide, or the residue of a 20 - keto - Δ^4 - (3 - keto or [3,2-c]-pyrazolo) - 11 - (keto, hydroxy or acyloxy) - 17α - (hydroxy or acyloxy) - 16α,21 - dihydroxy steroid of the pregnane series from which the 16α-hydroxy group has been removed.

9. 11β,17α - Dihydroxy - 1,4 - pregnadiene - 3,20 - dione - 21 - yl - β - D - 2' - acetamido - 2' - deoxyglucoside.

10. 16α - Methyl - 11β,17α - dihydroxy - 1,4 - pregnadiene - 3,20 - dione - 21 - yl - β - D - 2' - acetamido - 2' - deoxyglucoside.

11. 9α - Fluoro - 6α,16α - dimethyl - 11β,17α - dihydroxy - 1,4 - pregnadiene - 3,20 - dione - 21 - yl - β - D - 2' - acetamido - 2' - deoxyglucoside.

12. 9α - Fluoro - 16β - methyl - 11β,17α - dihydroxy - 1,4 - pregnadiene - 3,20 - dione - 21 - yl - β - D - 2' - acetamido - 2' - deoxyglucoside.

13. 6α - Methyl - 11β,17α - dihydroxy - 1,4 - pregnadiene - 3,20 - dione - 21 - yl - β - D - 2' - acetamido - 2' - deoxyglucoside.

14. 6α - Fluoro - 11β,17α - dihydroxy - 1,4 - pregnadiene - 3,20 - dione - 21 - yl - β - D - 2' - acetamido - 2' - deoxyglucoside.

15. 6,16α - Dimethyl - 11β,17α - dihydroxy - 4,6 - pregnadiene-3,20-dione-21-yl- β - D - 2' - acetamido - 2' - deoxyglucoside.

16. 9α - Fluoro - 11β,16α,17α - trihydroxy - 1,4 - pregnadiene - 3,20 - dione - 21 - yl - β - D - 2' - acetamido - 2' - deoxy - glucoside and the 4' - epimer thereof.

17. 6,16α - Dimethyl - 11β,17α - dihydroxy - [3,2-c]pyrazolo - 4,6 - pregnadien-20 - one - 21 - yl - β - D - 2' - acetamido - 2' - deoxyglucoside.

18. 11β,17α - Dihydroxy - (2' - phenyl - [3,2-c] - pyrazolo) - 4 - pregnen - 20 - one - 21 - yl - β - D - 2' - acetamido - 2' - deoxyglucoside.

19. 11β,17α - Dihydroxy - 1,4 - pregnadiene - 3,20 - dione - 21 - yl - tri - O - acetyl - β - D - 2' - acetamido - 2' - deoxyglucoside.

20. 16α - Methyl - 11β,17α - dihydroxy - 1,4 - pregnadiene - 3,20 - dione - 21 - yl - tri - O - acetyl - β - D - 2' - acetamido - 2' - deoxyglucoside.

21. 9α - Fluoro - 6α,16α - dimethyl - 11β,17α - dihydroxy - 1,4 - pregnadiene - 3,20 - dione - 21 - yl - tri - O - acetyl - β - D - 2' - acetamido - 2' - deoxyglucoside.

22. 9α - Fluoro - 16β - methyl - 11β,17α - dihydroxy - 1,4 - pregnadiene - 3,20 - dione - 21 - yl - tri - O - acetyl - β - D - 2' - acetamido - 2' - deoxyglucoside.

23. 6α - Methyl - 11β,17α - dihydroxy - 1,4 - pregnadiene - 3,20 - dione - 21 - yl - tri - O - acetyl - β - D - 2' - acetamido - 2' - deoxy - glucoside.

24. 6α - Fluoro - 11β,17α - dihydroxy - 1,4 - pregnadiene - 3,20 - dione - 21 - yl- tri - O - acetyl - β - D - 2' - acetamido - 2' - deoxyglucoside.

25. 6,16α - Dimethyl - 11β,17α - dihydroxy - 4,6 - pregnadiene - 3,20 - dione - 21 - yl - tri - O - acetyl - β - D - 2' - acetamido - 2' - deoxyglucoside.

26. 9α - Fluoro - 11β,16α,17α - trihydroxy - 1,4 - pregnadiene - 3,20 - dione - 21 - yl - tri - O - acetyl - β - D - 2' - acetamido - 2' - deoxyglucoside and the 4' - epimer thereof.

27. 6,16α - Dimethyl - 11β,17α - dihydroxy - [3,2-c] - pyrazolo - 4,6 - pregnadien - 20 - one - 21 - yl - tri - O - acetyl - β - D - 2' - acetamido-2'-deoxyglucoside.

28. 11β,17α - Dihydroxy - (2' - phenyl - [3,2-c] - pyrazolo) - 4 - pregnen - 20 - one - 21 - yl - tri - O - acetyl - β - D - 2' - acetamido - 2' - deoxyglucoside.

29. 9α - Fluoro - 11β,17α,21 - trihydroxy - 4 - pregnene - 3,20 - dione - 16α - yl - β - D - 2' - acetamido -2' - deoxyglucoside.

30. 9α - Fluoro - 11β,17α,21 - trihydroxy - 1,4 - pregnadiene - 3,20 - dione - 16α - yl - β - D - 2' - acetamido - 2' - deoxyglucoside.

31. 9α - Fluoro - 11β,17α,21 - trihydroxy - 4 - pregnene - 3,20 - dione - 16α - yl- tri - O - acetyl - β - D - 2' - acetamido - 2' - deoxyglucoside.

32. 9α - Fluoro - 11β,17α,21 - trihydroxy - 1,4 - pregnadiene - 3,20 - dione - 16α - yl - tri - O - acetyl - β - D - 2' - acetamido - 2' - deoxyglucoside.

33. A process for preparing a compound as claimed in claim 7, substantially as hereinbefore described with reference to Example 1 or 2.

34. A compound as claimed in claim 7, when prepared by a process as claimed in any one of claims 1—6 and 33 or by an obvious chemical equivalent of such a process.

35. A pharmaceutical composition comprising a pharmacologically acceptable carrier and a compound as claimed in any one of claims 7 and 9—18.

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COMPLETE SPECIFICATION

Steroid 2'-Acylamino-2'-Deoxy-Glucosides and -Galactosides

ERRATA

SPECIFICATION No. 1,059,548

Page 3, line 46, *for* "procdure" *read* "procedure"
Page 3, line 62, *for* "(as 0°)" *read* "(at 0°)"
Page 5, line 6, *for* "1-allopregnene" *read* "4-pregnene"
Page 6, lines 16 and 17, *for* "deoxygluside]" *read* "deoxyglucoside]"

THE PATENT OFFICE
5th April 1967

where R is a C_{1-3} alkanoyl radical and Z represents the residue of a 20 - keto - Δ^5 - (3 - keto or [3,2-c] - pyrazolo) - 11 - (keto, hydroxy or acyloxy) - 17α - (hydroxy or acyloxy) - 21 - hydroxy - steroid of the pregnane series from which the 21 - hydroxy group has been removed and in which any 16-hydroxy group is in free alcohol form or is formed, together with a 17α-hydroxy group, into a 16,17-acetomide, or the residue of a 20 - keto - Δ^4 - (3 - keto or [3,2-c] - pyrazolo) - 11 - (keto, hydroxy or acyloxy) - 17α - (hydroxy or acyloxy) - 16α,21 - dihydroxy steroid of the pregnane series from which the 16α-hydroxy group has been removed. Compounds represented by Formula I are glucoside derivatives and those represented by Formula II are galactoside derivatives. These novel steroid derivatives particularly 21-glucosides and 21-galactosides, possess the anti-inflammatory activity characteristic of cortisone but differ from cortisone, hydrocortisone, and their Δ^1 derivatives, prednisone and prednisolone, in being remarkably free from the ulcerogenic action, adrenal atrophy, thymus involution and body weight loss side-effects which have resulted from prolonged administration of the aforementioned anti-inflammatory steroids.

The invention also provides the tri-O-(C_{1-3} alkanoyl) derivatives of the novel 21-glucosides and their 4'-epimers.

In accordance with the present invention, the 2' - (C_{1-3} alkanoylamino) - 2' - deoxyglucoside of a 20 - keto - Δ^4 - (3 - keto or [3,2-c]pyrazolo) - 11 - (keto, hydroxy or acyloxy) - 17α - (hydroxy or acyloxy) - 21 - hydroxy - steroid of the pregnane series in which any 16 - hydroxy group is protected, e.g. by formation of a 16,17 - acetonide, or its 4' - epimer, is prepared by reacting the steroid with a 1 - halo - N - (C_{1-6} alkanoyl) - glucosamine tri(C_{1-6} alkanoate) or its 4'-epimer, thereby forming the tri-

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